UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,574	11/09/2001	Cesare Peschle	9855-26U3	3808

570 7590 02/03/2006

AKIN GUMP STRAUSS HAUER & FELD L.L.P.
ONE COMMERCE SQUARE
2005 MARKET STREET, SUITE 2200
PHILADELPHIA, PA 19103

EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 02/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/007,574	PESCHLE, CESARE	
	Examiner	Art Unit	
	Michail A. Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11,13-17 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11,13-17 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Claims 1-9, 11, 13-17 and 46 are pending.

Claims 1-9, 11, 13-17 and 46 are under consideration in the instant application.

2. The filing date of the instant claims is deemed to be the filing date of the instant applications, i.e. 11/09/2001, as the parent application 09/322,352 does not support the claimed method of generating a differentiated human cell of a selected type, comprising maintaining an isolated human KDR^+ stem cell in the presence of a differentiated mammalian cell of the selected type, the limitations of the instant application. If applicants disagree, applicants should present a detailed analysis as to why the claimed subject matter has clear support in the parent application.

In view of the amendment, filed 11/21/05 , the following rejections remain:

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-9, 11, 13-17, and 46 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of *in vitro* generation of a differentiation mammalian cells, wherein differentiated mammalian cells is selected from the group consisting of a skeletal muscle cell, an endothelial ells and hematopoietic cell, comprising maintaining an isolated human KDR+ stem cells in the medium in the presence of the differentiated mammalian cell, does not reasonably provide enablement for a method of *in vivo* generating a differentiated human cell of any selected type , the method comprising maintaining an isolated human KDR+ stem cell in the presence of a differentiated any mammalian cell of the selected type as claimed in claims 1-9, 11, 13-17 or maintaining an isolated human KDR+ stem cell in a medium conditioned to reflect the presence of differentiated mammalian cells of the selected type, as claimed in claim 46. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action, mailed on 05/18/05.

Applicant's arguments, filed 11/21/05 have been fully considered, but have not been found convincing.

Applicant asserts that : (i) the examples themselves and the extensive citation of references would be more than adequate to enable a person skill in the art to use the invention both in vitro and in vivo; (ii) Waller et al., position is not prevalent, because skill in the art recognize that there is evidence that a single cell can differentiate along both hematopoietic and stromal lineage (iii) the specification disclosed how to achieve highly homogenous population by the isolated techniques, as further supported by Fig. 1E and 1F; (iv) Example 2 shows in vitro evidence that the CD34+KDR+ cells results in both hematopoietic and endothelial cell precursors; (v) example 3-5 provided evidences that the CD34+KDR+ cells differentiate into other tissues.

It's remains the Examiner position that the Specification does not reasonably provide enablement for a method of *in vivo* generating a differentiated human cell of any selected type , the method comprising maintaining an isolated human KDR+ stem cell in the presence of a differentiated any mammalian cell of the selected type as claimed.

With regards to the issue (ii). It is the examiner position that based on the finding reported in Waller et al., that there is no solid evidence for a hypothesis of a "common stem cell" (see page 2422 in particular) the skilled artisan would not recognized that a single cell can differentiate along both hematopoietic and stromal lineage. Based on the analysis of over 30,000 stem cells with a variety of CD34+ phenotypes and 864 stromal culture, Waller et al. concluded that the is no evidence that a single cell can differentiate along both a hematopoietic and stromal lineage (see page 2434 in particular). Moreover, it is noted that CD34+KDR+ cells would be present in CD34+ cells taught by Waller et al., as evidenced by Ziegler et al (IDS). It is also not clear from the Specification how it was asserted that the injected human donor post natal CD34+KDR+ cells differentiated into any specific cell type as claimed in claim 17.

With regards to the issue (iii). The Specification on page 49 paragraph 0169 clearly stated that a KDR^{dim} subpopulation has been identified in CD34+ cells and co-sorted with the KDR^{bright} fraction. These corroborate the Examiner's position that it is very possible that the cell population contain heterogeneous cell population that give rise to both hemopoietic and stromal elements. What was the sensitivity of the method for selecting natal CD34+KDR+ primitive stem cell, what is the accurate and reproducible quantification of such selection. One skilled in the art would not know the homogeneous nature of the natal CD34+KDR+ primitive stem cell using the teaching of the specification alone. Moreover, there is no evidence from the Specification that there was no fusion of the $CD34^{+}KDR^{+}$ cells with cells of the other lineages. Holden et al. (Science, 2002, V.296, pages 2126-2129) teach that cells can mutate and develop markers characteristics of other lineages or that cells injected into a foreign tissue can take up local DNA and thus appears to have changes identity (see page 2126 in particular). Moreover, Holden et al., further teach that fusion scare has given further impetus to effort to establish rigorous standards for demonstrating plasticity such as: the cells must be properly identified at the outset, because a single alien cell in ostensibly purified culture could produce misleading

results. The cells must contribute to the function of the host tissue. There is no indication that demonstrate functionality of said cells in the specification.

With regards to Examples 2 - 5 of the current Specification.

It is noted that the data of the Example 2 clearly demonstrated that *in vitro* post natal $CD34^{+}KDR^{+}$ are capable of differentiation into cells at sequential stages of differentiation that shows the cell markers of endothelial cells. However, this experiment was done at very specific serum-free liquid suspension culture, without the presence of : (i) a differentiated mammalian cell of the selected type or (ii) a medium conditioned to reflect the presence of differentiated mammalian cells of the selected type, as claimed in the instant claims. The mere fact that stem cells *in vitro* are capable for differentiation was well known at the time of the invention. In the examples 4 and 5 the post natal CD34+KDR+ cells were injected in non-immunocompromised murine blastocytes and the fate of the injected human cells during murine embriogenesis and post-natal life was followed (see Example 4 of the Specification as filed) or injected into the regenerating muscle (see Example 5 of the Specification in particular).

However, the issue raised in the previous Office Action was that that the specification does not teach how to extrapolate data obtained from above discussed limited studies to the development of effective *in vivo* methods of generating a differentiated human cell of a specific selected type, such as the recited in claim 17, wherein isolated human KDR+ stem cells are maintained in the presence of differentiated mammalian cell or in a medium conditioned to reflect the presence of any differentiated mammalian cells, whereby the stem cell differentiated to become the differentiated human cell of the selected type, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of a methods of generating a differentiated human cell of a specific selected type, such as recited in claim17, wherein isolated human KDR+ stem cells are maintained in the presence of any differentiated mammalian cell or in a medium conditioned to reflect the presence of any differentiated mammalian cells, whereby the stem cell differentiated to become the differentiated human cell of the selected type.

Moreover, recently published journal articles by Botta et al., and Pelosi et al., corroborate the examiner position that *in vitro* data can not be extrapolated to generate *in vivo* differentiated mammalian cells of selected type. For example, Botta et al., clearly stated that whether human CD34+ progenitor can be induced to differentiate in vivo into CMCs is not known yet. Similarly, Pelosi et al ., teach that within the Cd34+KDR+ population the cell subsets endowed with hemangioblast activity and plastic capacity may partially or totally overlap postnatal hemangoiblasts hypothetically represent residual embryonic stem cells with wide-spectrum differentiation potential. Further studies based on hemangioblast purification and in vivo assay will be required.

Thus the specification fails to demonstrate that isolated human KDR+ stem cells in vivo can be generated to differentiate into any differentiated human cell by maintaining an isolated human KDR+ stem cell in the presence of a differentiated mammalian cell of the selected type as

claimed in claims 1-9, 11, 13-17 or maintaining an isolated human KDR+ stem cell in a medium conditioned to reflect the presence of differentiated mammalian cells of the selected type, as claimed in claim 46 and the art does not recognize that a single cell can differentiate along both a hematopoietic and stromal lineage. The courts have held that it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. (Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001).

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed for a method of *in vivo* generating a differentiated human cell of any selected type , the method comprising maintaining an isolated human KDR+ stem cell in the presence of a differentiated any mammalian cell of the selected type as claimed in claims 1-9, 11, 13-17 or maintaining an isolated human KDR+ stem cell in a medium conditioned to reflect the presence of differentiated mammalian cells of the selected type, as claimed in claim 46. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

6. Claims 1-9, 11, 13-17 and 46 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bruder et al (US Paten NO:5,736396) in view of Lemischka (US Patent 5,912133) and as evidenced by the Specification disclosure on page 63, lines 4-8 and page 4, lines 4-10 and newly cited Labastie et al (Blood, 1998, V.92, pages 3624-3635) for the same reasons set forth in the previous Office Action, mailed on 05/18/05.

Applicant's arguments, filed 11/21/05 have been fully considered, but have not been found convincing.

Applicant asserts that: the is no suggestion to combine the teaching of US Patent '396 and US Patent '133 and the combination appears to have been based on the hindsight provided by Applicant's own application as the Examiner specifically relied on two statements from the application.

In response to applicant's arguments that there is no suggestion to combine the references, and that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 170 USPQ 209 (CCPA 1971). In addition, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992). The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144

In this case, US Patent '396 teaches a method of generating a differentiated cell of a selected type by incubation human mesenchymal stem cells in the presence of differentiated mammalian cells or condition medium that are effective to induce differentiation into a lineage of choice.(see entire document, Abstract , Column 1, lines 50-55 and Fig.1 in particular). US Patent '396 teaches that human mesenchymal stem cells can be isolated from various tissues that contained stem cells (see column 4 , lines 10-65 in particular). US Patent '396 teaches that human mesenchymal stem cells can be either injected at the site of skeletal defects or incubated in the presence of differentiated cells (see column 5, lines 11-20 in particular).

US Patent '396 does not teach that stem cells are human KDR^+ stem cells.

US Patent '133 teaches a method of isolating human FLK^+ stem cells using antibody that specifically binds FLK-1 (see entire document, Abstract in particular). The Specification on page 63, lines 4-8 disclosed that human KDR^+ stem cells are the same subpopulation of $CD34^+$ of cells as human FLK^+ stem cells. US Patent '133 teaches that human FLK^+ stem cells can be obtained from various tissues that contained stem cells (see column 14, lines 20-50). US Patent

'133 teaches that isolated human FLK^+ stem cells have an ability to differentiate *in vitro* or *in vivo*. This ability has an important therapeutic applications (see overlapping column 7 and 8 in particular).

The Examiner respectfully disagrees with Applicant's statement that " the rejection has been based on the hindsight provided by Applicant's own application as the Examiner specifically relied on two statements from the application". Said two passages from the instant application have been cited in the previous Office Action to corroborate the examiner position that it was general knowledge in the art that human FLK^+ cells is the same subpopulation as human KDR^+ cells. This is not Applicant's invention but rather well known concept in the art, as is evidenced by newly cited Labastie et al. Labastie et al., teach that HSCs associated with the 5-week human embryo are flk-1/KDR positive (see entire document, page 3632 in particular). In other words, it was well known in the art that FLK+ stem cells is the same subpopulation as KDR+ stem cells.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '133 to those of US Patent '396 and substitute isolated human mesenchymal stem cells to isolating human KDR^+ stem cells to obtain a claimed method of generating a differentiated human cell of a selected type comprising maintaining an isolated KDR+ stem cells in the presence of a differentiated mammalian cells of the selected type.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because isolated human KDR^+ stem cells can be induced to differentiate *in vitro* or *in vivo* and this ability has an important therapeutic applications as taught by US Patent '133 . This subpopulation of human stem cells can be used to generated a differentiated human cell of a selected type by the method taught by US Patent '396 .

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim 4 is included because this functional limitation would be an obvious variation of the method using a condition media taught by US Patent '396. It will be immediately obvious to one skill in the art that the use a porous barrier, having pores of a size sufficient to allow the passage of a small proteins but not stem cells as claimed in claim 4 will result in obtaining a condition medium as taught by US Patent '396. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum conditions involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

Claims 6-10 are included because it would be conventional and within the skill of the art to identify various tissues that contained KDR^+ stem cells and used KDR1 and KDR2 antibody that were known and readily available to a person of ordinary skill in the art at the time the invention was made (see Applicant's arguments, filed 1/29/04, page 8 in particular) . In addition, Applicant himself acknowledge that any tissue that contains stem cells can be used (see page 4, line 4-10 of the instant Specification in particular). Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges or conditions involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

Claims 14-16 are included because it would be obvious , conventional and within the skill of the art to use differentiated mammalian cells of different origin, since US Patent '396 teaches a method of generating a differentiated cell of into a lineage of choice. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges or conditions involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

7. No claim is allowed

8. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/ 272-0841 .

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michail Belyavskyi, Ph.D.
Patent Examiner
Technology Center 1600
January 20,2006

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600